```
=> file caplus; d que l5
FILE 'CAPLUS' ENTERED AT 17:50:32 ON 02 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 2 Mar 2004  VOL 140 ISS 10
FILE LAST UPDATED: 1 Mar 2004  (20040301/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L1             3 SEA FILE=CAPLUS ABB=ON  PLU=ON  (MURAMATSU A?/AU OR OKAMOTO
                 K?/AU) AND KUMAI H?/AU
L2            31 SEA FILE=CAPLUS ABB=ON  PLU=ON  (MURAMATSU A?/AU OR OKAMOTO
                 K?/AU OR ODA M?/AU) AND (KUMAI H?/AU OR IKEMATSU S?/AU OR
                 SAKUMA S?/AU)
L3            28 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2 NOT L1
L4             3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND (?TUMOR? OR ?TUMOUR? OR
                 ?CANCER? OR ?CARCINO? OR ?NEOPL?)
L5             6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L1 OR L4


=> file medline; d que l38
FILE 'MEDLINE' ENTERED AT 17:50:41 ON 02 MAR 2004

 FILE LAST UPDATED: 25 FEB 2004 (20040225/UP). FILE COVERS 1953 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L38            2 SEA FILE=MEDLINE ABB=ON  PLU=ON  (MURAMATSU A?/AU OR OKAMOTO
                 K?/AU) AND KUMAI H?/AU


=> file embase; d que l43
FILE 'EMBASE' ENTERED AT 17:50:52 ON 02 MAR 2004
```

FILE COVERS 1974 TO 26 Feb 2004 (20040226/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
L41           7 SEA FILE=EMBASE ABB=ON  PLU=ON  (MURAMATSU A?/AU OR OKAMOTO
                K?/AU OR ODA M?/AU) AND (KUMAI H? OR IKEMATSU S? OR SAKUMA
                S?)/AU
L42         191 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L43           2 SEA FILE=EMBASE ABB=ON  PLU=ON  L41 AND L42
```

```
=> file biosis; d que l62
FILE 'BIOSIS' ENTERED AT 17:51:02 ON 02 MAR 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 25 February 2004 (20040225/ED)

FILE RELOADED: 19 October 2003.
```

```
L55         351 SEA FILE=BIOSIS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                MK
L61          10 SEA FILE=BIOSIS ABB=ON  PLU=ON  (MURAMATSU A?/AU OR OKAMOTO
                K?/AU OR ODA M?/AU) AND (KUMAI H? OR IKEMATSU S? OR SAKUMA
                S?)/AU
L62           5 SEA FILE=BIOSIS ABB=ON  PLU=ON  L61 AND L55
```

```
=> file wpid; d que l68
FILE 'WPIDS' ENTERED AT 17:51:11 ON 02 MAR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE LAST UPDATED:          2 MAR 2004      <20040302/UP>
MOST RECENT DERWENT UPDATE:     200415        <200415/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM
    DERWENT UPDATE 200403.
    THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
```

SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<

L66 8 SEA FILE=WPIDS ABB=ON PLU=ON (MURAMATSU A?/AU OR OKAMOTO K?/AU OR ODA M?/AU) AND (KUMAI H? OR IKEMATSU S? OR SAKUMA S?)/AU
L67 67 SEA FILE=WPIDS ABB=ON PLU=ON MIDKINE OR MDK PROTEIN OR GENE MK
L68 4 SEA FILE=WPIDS ABB=ON PLU=ON L66 AND L67

=> dup rem l38 l5 l43 l62 l68
FILE 'MEDLINE' ENTERED AT 17:51:45 ON 02 MAR 2004

FILE 'CAPLUS' ENTERED AT 17:51:45 ON 02 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 17:51:45 ON 02 MAR 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE 'BIOSIS' ENTERED AT 17:51:45 ON 02 MAR 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'WPIDS' ENTERED AT 17:51:45 ON 02 MAR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT
PROCESSING COMPLETED FOR L38
PROCESSING COMPLETED FOR L5
PROCESSING COMPLETED FOR L43
PROCESSING COMPLETED FOR L62
PROCESSING COMPLETED FOR L68
L81 10 DUP REM L38 L5 L43 L62 L68 (9 DUPLICATES REMOVED)
ANSWERS '1-2' FROM FILE MEDLINE
ANSWERS '3-6' FROM FILE CAPLUS
ANSWERS '7-9' FROM FILE BIOSIS
ANSWER '10' FROM FILE WPIDS

=> d ibib ab ed l81 1-10

L81 ANSWER 1 OF 10 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003277137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12804566
TITLE: High levels of urinary midkine in various cancer patients.
AUTHOR: Ikematsu Shinya; **Okamoto Kohji**; Yoshida Yoshihiro; Oda Munehiro; Sugano-Nagano Hitomi; Ashida Kinya; **Kumai Hideshi**; Kadomatsu Kenji; Muramatsu Hisako; Takashi Muramatsu; Sakuma Sadatoshi
CORPORATE SOURCE: Meiji Dairies Corporation, 540 Naruda, Odawara, Kanagawa 250-0862, Japan.
SOURCE: Biochemical and biophysical research communications, (2003 Jun 27) 306 (2) 329-32.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030614
Last Updated on STN: 20030726
Entered Medline: 20030725

AB Midkine (MK) is a heparin-binding growth factor, which promotes growth, migration, and survival of various cells, and MK expression is increased in many human carcinomas. We determined the urinary MK level by enzyme-linked immunoassay. Taking 311pg/mg creatinine as a cut-off level, 70% of patients with various carcinomas (n=142) gave positive values, while only 5.5% of healthy volunteers (n=330) did. In case of gastric carcinoma, 17 out of 21 patients with stage 1 tumor were positive. Urinary MK levels are expected to become a convenient marker as an aid in detection of tumors.

ED Entered STN: 20030614
Last Updated on STN: 20030726
Entered Medline: 20030725

L81 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2000454571 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10952771
TITLE: Serum midkine levels are increased in patients with various types of carcinomas.
AUTHOR: Ikematsu S; Yano A; Aridome K; Kikuchi M; **Kumai H**; Nagano H; **Okamoto K**; Oda M; Sakuma S; Aikou T; Muramatsu H; Kadomatsu K; Muramatsu T
CORPORATE SOURCE: Meiji Cell Technology Center, 540 Naruda, Odawara, 250-0862, Japan.
SOURCE: British journal of cancer, (2000 Sep) 83 (6) 701-6. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928

AB The level of expression of midkine (MK), a heparin-binding growth factor, is increased in many types of human carcinomas. An enzyme-linked immunoassay, which utilizes a combination of rabbit and chicken antibodies revealed that serum MK level in the controls (n = 135) was 0.154 +/- 0.076 (mean +/- SD) ng ml(-1)with an apparent cut-off value as 0.5 ng ml(-1). Serum MK level was significantly elevated in the cancer patients (n = 150) (P< 0.001); 87% of the patients showed levels of more than 0.5 ng ml(-1). All ten types of cancer examined showed a similar profile of serum MK level. There was no or weak correlation between C-reactive protein level, a marker of inflammation, and serum MK level. Furthermore, in case of gastric carcinoma and lung carcinoma, patients with stage I carcinoma already showed elevated serum MK levels. The present results indicated that serum MK could serve as a general tumour marker with a good potential for clinical application.

ED Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928

L81 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2001:208510 CAPLUS
DOCUMENT NUMBER: 134:204750
TITLE: Early cancer diagnosis using midkine as tumor marker

INVENTOR(S): Muramatsu, Takashi; **Okamoto, Kohji**; Ikematsu, Shinya; Oda, Munehiro; **Kumai, Hideshi**; Sakuma, Sadatoshi
PATENT ASSIGNEE(S): Meiji Milk Products Co., Ltd, Japan
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001020333	A1	20010322	WO 2000-JP6147	20000908
W: AU, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1215500	A1	20020619	EP 2000-957049	20000908
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				

PRIORITY APPLN. INFO.:
JP 1999-256678 A 19990910
JP 1999-345404 A 19991203
JP 2000-33168 A 20000210
WO 2000-JP6147 W 20000908

AB It is found out that MK (midkine) appears in the blood or urine of patients with various cancers (e.g., stomach cancer, hepatocellular carcinoma, lung cancer) in their early stages. Based on this finding, a method is completed for diagnosing an early cancer by immunol. measuring MK and/or its fragment in the blood or urine sample.
ED Entered STN: 22 Mar 2001
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L81 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2000:53419 CAPLUS
DOCUMENT NUMBER: 132:73672
TITLE: Midkine proteins as remedies for apoptosis-associated diseases
INVENTOR(S): Muramatsu, Takashi; **Ikematsu, Shinya**; Yoshida, Yoshihiro; Kadomatsu, Kenji; **Oda, Munehiro**; **Sakuma, Sadatoshi**; Ashida, Kin-ya; Kino, Kohsuke
PATENT ASSIGNEE(S): Meiji Milk Products Co., Ltd., Japan
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000002578	A1	20000120	WO 1999-JP3740	19990709
W: AU, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2343746	AA	20000120	CA 1999-2343746	19990709
AU 9946507	A1	20000709	AU 1999-46507	19990709
AU 761418	B2	20030605		
EP 1097717	A1	20010509	EP 1999-929785	19990709

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: JP 1998-210297 A 19980710
JP 1998-284760 A 19980922
WO 1999-JP3740 W 19990709

AB It is found out that a protein belonging to the midkine (MK) family inhibits the induction of apoptosis caused by **anticancer** agents, UV irradiation and ischemic stress. This finding makes it possible to provide novel drugs containing the protein belonging to the MK family as the active ingredient for treating and preventing any diseases caused by apoptosis, for example, heart diseases, renal diseases, nervous diseases or liver diseases.

ED Entered STN: 23 Jan 2000
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L81 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1998:621130 CAPLUS
DOCUMENT NUMBER: 129:197990
TITLE: Preventive and therapeutic compositions for drug-induced nephropathy and hepatitis
INVENTOR(S): Muramatsu, Takashi; Kadomatsu, Kenji; **Oda, Munehiro; Ikematsu, Shinya; Sakuma, Sadatoshi**
PATENT ASSIGNEE(S): Meiji Milk Products Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9840095	A1	19980917	WO 1998-JP1050	19980312
W: AU, CA, CN, ID, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9863105	A1	19980929	AU 1998-63105	19980312
AU 738923	B2	20010927		
EP 997150	A1	20000503	EP 1998-907207	19980312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2002019333	A1	20020214	US 1999-380882	19991202
US 6572851	B2	20030603		

PRIORITY APPLN. INFO.: JP 1997-74684 A 19970312
WO 1998-JP1050 W 19980312

AB The invention relates to novel agents for relieving drug-induced nephropathy and acute hepatitis, containing proteins belonging to the midkine (MK) family, e.g., pleiotrophin (PTN). The proteins belonging to the MK family can inhibit nephropathy induced by **antineoplastic** agents such as cisplatin or acute hepatitis due to carbon tetrachloride, thus being effective in relieving drug-induced nephropathy or hepatitis.

ED Entered STN: 01 Oct 1998
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L81 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:375060 CAPLUS
DOCUMENT NUMBER: 122:142611

TITLE: Coated hydroxyapatite particles as carriers for adsorption of physiologically active substances, pharmaceutical preparations containing the particles, and stabilization of dispersions containing hydroxyapatite particles by coating with albumin and/or polycarboxylic acids
INVENTOR(S): **Oda, Munehiro**; Yokoyama, Minehiko; Ikegami, Hideji; **Sakuma, Sadatoshi**; Ito, Hiroyuki
PATENT ASSIGNEE(S): Meiji Milk Prod Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06329557	A2	19941129	JP 1993-120015	19930521

PRIORITY APPLN. INFO.: JP 1993-120015 19930521

AB Carriers, for adsorption of physiol. active substances and useful for pharmaceutical prepns., comprise fine hydroxyapatite (I) particles (average particle size ≤500 nm) coated with albumin and/or polycarboxylic acids. Aqueous suspension containing I (1 mg/mL) was treated with human serum albumin (HSA) (0.5 mg/mL) to show good dispersibility and average particle size 0.06 μm, vs. 0.78 μm, for control treated with gelatin instead of HSA. A composition (particle size ≤150 nm) containing I (7.4 mg/mL) treated with HSA (1.5 mg/mL) showed LD50 of ≥250 mg/kg i.v. in mice, vs. 70-90 mg/kg, for a control (average particle size >500 nm). Murine antibodies and Ca-binding protein (CBP)-bound neocarzinostatin (NCS) were adsorbed on I and the composition was treated with HSA to give an **anticancer** preparation Mice were administered with the preparation (0.27 mg I, 2.7 μg CBP-NCS, and 13.4 μg albumin) i.p. at the day 1 and day 2 after i.p. transplantation of leukemia cells BALBRV 4 to show survival rate of .apprx.60% 50 days later, vs. 20% for controls administered with a preparation containing CBP-NCS and albumin, but not I.
ED Entered STN: 25 Feb 1995

L81 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:302742 BIOSIS
DOCUMENT NUMBER: PREV200300302742
TITLE: Method for suppressing or treating drug-induced nephropathy.
AUTHOR(S): Muramatsu, Takashi [Inventor, Reprint Author]; Kadomatsu, Kenji [Inventor]; **Oda, Munehiro** [Inventor]; **Ikematsu, Shinya** [Inventor]; **Sakuma, Sadatoshi** [Inventor]
CORPORATE SOURCE: Aichi, Japan
ASSIGNEE: Takashi Muramatsu, Japan
PATENT INFORMATION: US 6572851 June 03, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 3 2003) Vol. 1271, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003

AB The present invention provides a novel drug for relieving drug-induced nephropathy and acute hepatopahy containing a **midkine** (MK)

family protein such as pleiotrophin (PTN). The MK family proteins can inhibit nephropathy induced by an antitumor agent or acute hepatopathy caused by carbon tetrachloride and thus effectively relieve drug-induced nephropathy or hepatopathy.
ED Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003

L81 ANSWER 8 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:334513 BIOSIS
DOCUMENT NUMBER: PREV200200334513
TITLE: Composition comprising **midkine** or pleiotrophin protein and method of increasing hematopoietic cells.
AUTHOR(S): Kikuchi, Makoto [Inventor, Reprint author]; **Ikematsu, Shinya** [Inventor]; **Oda, Munehiro** [Inventor]; **Sakuma, Sadatoshi** [Inventor]; Muramatsu, Takashi [Inventor]
CORPORATE SOURCE: Fukuoka, Japan
ASSIGNEE: Meiji Milk Products, Co., Ltd., Tokyo, Japan
PATENT INFORMATION: US 6383480 May 07, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jun 2002
Last Updated on STN: 12 Jun 2002
AB The present invention provides novel use of the MK family that is used alone as an agent for proliferating hematopoietic stem cells and hematopoietic precursor cells. The invention also provides an agent for remarkably enhancing the above-described effect for promoting the proliferation of hematopoietic stem cells and hematopoietic precursor cells, comprising the MK family in combination with known hematopoietic factors such as IL-3, IL-6, G-CSF, GM-CSF, M-CSF, SCF, and EPO.
ED Entered STN: 12 Jun 2002
Last Updated on STN: 12 Jun 2002

L81 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:158755 BIOSIS
DOCUMENT NUMBER: PREV200100158755
TITLE: Treatment of peptic ulcers using **midkine** (MK) proteins.
AUTHOR(S): Uchida, Masayuki [Inventor, Reprint author]; **Ikematsu, Shinya** [Inventor]; Yokoyama, Minehiko [Inventor]; Yamashita, Akio [Inventor]; **Kumai, Hideshi** [Inventor]; **Oda, Munehiro** [Inventor]; Kato, Naoki [Inventor]; **Sakuma, Sadatoshi** [Inventor]; Muramatsu, Takashi [Inventor]
CORPORATE SOURCE: Kanagawa, Japan
ASSIGNEE: Meiji Milk Products Co., Ltd., Tokyo, Japan
PATENT INFORMATION: US 6083907 July 04, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 4, 2000) Vol. 1236, No. 1. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Mar 2001
Last Updated on STN: 15 Feb 2002
AB An anti-ulcer composition is provided, which comprises as an active ingredient at least one of MK protein, its derivative having biological

activity of MK protein, and their fragment having biological activity of MK protein, and a pharmaceutically acceptable carrier. The composition exhibits an effect for treating ulcer by promoting autotherapy without recurrence of ulcer.

ED Entered STN: 28 Mar 2001
Last Updated on STN: 15 Feb 2002

L81 ANSWER 10 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1999-263639 [22] WPIDS
DOC. NO. CPI: C1999-077719
TITLE: Agent for treating or preventing ischemia or stress related cell disorders.
DERWENT CLASS: B04
INVENTOR(S): **IKEMATSU, S; ODA, M; SAKUMA, S**; YOSHIDA, Y
PATENT ASSIGNEE(S): (MEIP) MEIJI MILK PROD CO LTD; (YOSH-I) YOSHIDA Y; (YOSH-I) YOSHIHIRO Y
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9916463	A1	19990408	(199922)*	JA	42
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA CN JP KR US					
AU 9891851	A	19990423	(199935)		
EP 1057489	A1	20001206	(200064)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1278184	A	20001227	(200123)		
KR 2001030716	A	20010416	(200163)		
JP 2000513596	X	20020820	(200258)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9916463	A1	WO 1998-JP4299	19980925
AU 9891851	A	AU 1998-91851	19980925
EP 1057489	A1	EP 1998-944236	19980925
		WO 1998-JP4299	19980925
CN 1278184	A	CN 1998-810868	19980925
KR 2001030716	A	KR 2000-703223	20000325
JP 2000513596	X	WO 1998-JP4299	19980925
		JP 2000-513596	19980925

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9891851	A	Based on	WO 9916463
EP 1057489	A1	Based on	WO 9916463
JP 2000513596	X	Based on	WO 9916463

PRIORITY APPLN. INFO: JP 1997-279435 19970926
AB WO 9916463 A UPAB: 19990609
NOVELTY - Agent for treating or preventing ischemia or stress related cell disorders comprises a **midkine** family protein (MK).
ACTIVITY - Cerebroprotective; Nootropic; Antiparkinsonian
MECHANISM OF ACTION - None given.
USE - For treating or preventing ischemic diseases and related cell

injuries such as brain infarction, transient cerebral ischemia, cerebral ischemic attack and head injury. MK can also be used to treat cerebrovascular contraction following subarachnoid bleeding, Alzheimer's disease, senile dementia of the Alzheimer's type, cerebrovascular dementia and other cerebrovascular diseases, Parkinson's disease, Huntington's chorea and degenerative amyotrophic diseases.

Dwg.0/15

ED 19990609

```
=> file hcaplus; d que l14; d que l16; d que l20; d que l23; d que l25
FILE 'HCAPLUS' ENTERED AT 17:53:07 ON 02 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```


FILE COVERS 1907 - 2 Mar 2004 VOL 140 ISS 10
FILE LAST UPDATED: 1 Mar 2004 (20040301/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L6	352	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	MIDKINES+OLD/CT OR GENE MK
L8	8142	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	TUMOR MARKERS+PFT/CT
L14	19	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L6 AND L8

L6	352	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	MIDKINES+OLD/CT OR GENE MK
L9	14180	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	BIOMARKERS/CW OR BIOLOGICAL MARKERS
L12	663956	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	?NEOPLAS? OR ?CARCINO? OR ?TUMOR? OR TUMOUR? OR ?CANCER?
L16	2	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L6 AND L9 AND L12

L6	352	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	MIDKINES+OLD/CT OR GENE MK
L10	50549	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	DIAGNOSIS+PFT/CT
L12	663956	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	?NEOPLAS? OR ?CARCINO? OR ?TUMOR? OR TUMOUR? OR ?CANCER?
L18	23	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L6 AND L10 AND L12
L20	1	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L18 AND MONOCLONAL/TI

L6	352	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	MIDKINES+OLD/CT OR GENE MK
L11	47608	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	IMMUNOASSAY+OLD/CT
L12	663956	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	?NEOPLAS? OR ?CARCINO? OR ?TUMOR? OR TUMOUR? OR ?CANCER?
L22	3	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L6 AND L11 AND L12
L23	1	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	L22 AND IMMUNOASSAY/TI

L6	352	SEA	FILE=HCAPLUS	ABB=ON PLU=ON	MIDKINES+OLD/CT OR GENE MK

```
L11        47608 SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOASSAY+OLD/CT
L21            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND L11
L25            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 AND SANDWICH/TI

=> s (l14 or l16 or l20 or l23 or l25) not l5
           325 MURAMATSU A?/AU
          5437 OKAMOTO K?/AU
           126 KUMAI H?/AU
           325 MURAMATSU A?/AU
          5437 OKAMOTO K?/AU
          2137 ODA M?/AU
           126 KUMAI H?/AU
            63 IKEMATSU S?/AU
           721 SAKUMA S?/AU
           325 MURAMATSU A?/AU
          5437 OKAMOTO K?/AU
           126 KUMAI H?/AU
        432006 ?TUMOR?
          2528 ?TUMOUR?
        236221 ?CANCER?
        212500 ?CARCINO?
        367461 ?NEOPL?
L82            20 (L14 OR L16 OR L20 OR L23 OR L25) NOT L5

=> file medline; d que l36; d que l39
FILE 'MEDLINE' ENTERED AT 17:54:37 ON 02 MAR 2004

 FILE LAST UPDATED: 25 FEB 2004 (20040225/UP).  FILE COVERS 1953 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L26          233 SEA FILE=MEDLINE ABB=ON  PLU=ON  MIDKINE/CN
L27           10 SEA FILE=MEDLINE ABB=ON  PLU=ON  MDK PROTEIN, HUMAN/CN
L28            4 SEA FILE=MEDLINE ABB=ON  PLU=ON  MIDKINE RECEPTOR/CN
L29        78870 SEA FILE=MEDLINE ABB=ON  PLU=ON  TUMOR MARKERS, BIOLOGICAL+NT/C
                  T
L30       255398 SEA FILE=MEDLINE ABB=ON  PLU=ON  DIGESTIVE SYSTEM NEOPLASMS+NT/
                  CT
L31       129382 SEA FILE=MEDLINE ABB=ON  PLU=ON  RESPIRATORY TRACT NEOPLASMS+NT
                  /CT
L36            7 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L26 OR L27 OR L28) AND L29
                  AND (L30 OR L31)



L26          233 SEA FILE=MEDLINE ABB=ON  PLU=ON  MIDKINE/CN
L27           10 SEA FILE=MEDLINE ABB=ON  PLU=ON  MDK PROTEIN, HUMAN/CN
L28            4 SEA FILE=MEDLINE ABB=ON  PLU=ON  MIDKINE RECEPTOR/CN
L30       255398 SEA FILE=MEDLINE ABB=ON  PLU=ON  DIGESTIVE SYSTEM NEOPLASMS+NT/
```

L5 = inventors, previously displayed

```
                CT
L31       129382 SEA FILE=MEDLINE ABB=ON  PLU=ON  RESPIRATORY TRACT NEOPLASMS+NT
                 /CT
L33       257054 SEA FILE=MEDLINE ABB=ON  PLU=ON  IMMUNOASSAY+NT/CT
L39            6 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L26 OR L27 OR L28) AND L33
                 AND (L30 OR L31)
```

L38 = inventors, previously displayed

```
=> s (l36 or l39) not l38
L83           10 (L36 OR L39) NOT L38

=> file embase; d que l50; d que l51; d que l53
FILE 'EMBASE' ENTERED AT 17:55:15 ON 02 MAR 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

 FILE COVERS 1974 TO 26 Feb 2004 (20040226/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L42           191 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L44         13637 SEA FILE=EMBASE ABB=ON  PLU=ON  TUMOR MARKER/CT
L46        198873 SEA FILE=EMBASE ABB=ON  PLU=ON  DIGESTIVE SYSTEM TUMOR+NT/CT
L47         16952 SEA FILE=EMBASE ABB=ON  PLU=ON  LUNG CARCINOMA/CT OR LUNG
                  SARCOMA/CT
L50             4 SEA FILE=EMBASE ABB=ON  PLU=ON  L42 AND L44 AND (L46 OR L47)



L42           191 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L45          9544 SEA FILE=EMBASE ABB=ON  PLU=ON  BIOLOGICAL MARKER/CT
L46        198873 SEA FILE=EMBASE ABB=ON  PLU=ON  DIGESTIVE SYSTEM TUMOR+NT/CT
L47         16952 SEA FILE=EMBASE ABB=ON  PLU=ON  LUNG CARCINOMA/CT OR LUNG
                  SARCOMA/CT
L51             0 SEA FILE=EMBASE ABB=ON  PLU=ON  L42 AND L45 AND (L46 OR L47)



L42           191 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L46        198873 SEA FILE=EMBASE ABB=ON  PLU=ON  DIGESTIVE SYSTEM TUMOR+NT/CT
L47         16952 SEA FILE=EMBASE ABB=ON  PLU=ON  LUNG CARCINOMA/CT OR LUNG
                  SARCOMA/CT
L48        137793 SEA FILE=EMBASE ABB=ON  PLU=ON  IMMUNOASSAY+NT/CT
L53             5 SEA FILE=EMBASE ABB=ON  PLU=ON  L42 AND L48 AND (L46 OR L47)
```

L43 = inventors, previously displayed

```
=> s (l50 or l53) not l43
L84           4 (L50 OR L53) NOT L43

=> file biosis; d que l60; d que l63; d que l65
FILE 'BIOSIS' ENTERED AT 17:55:54 ON 02 MAR 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.
```

RECORDS LAST ADDED: 25 February 2004 (20040225/ED)

FILE RELOADED: 19 October 2003.

```
L55          351 SEA FILE=BIOSIS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                 MK
L56        40853 SEA FILE=BIOSIS ABB=ON  PLU=ON  BIOMARKER? OR (BIOLOGICAL OR
                 TUMOR OR NEOPLASM OR CARCINOGEN) (1A) MARKER
L60            6 SEA FILE=BIOSIS ABB=ON  PLU=ON  L55 AND L56


L55          351 SEA FILE=BIOSIS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                 MK
L57        59927 SEA FILE=BIOSIS ABB=ON  PLU=ON  IMMUNOASSAY
L63            6 SEA FILE=BIOSIS ABB=ON  PLU=ON  L55 AND L57


L55          351 SEA FILE=BIOSIS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                 MK
L56        40853 SEA FILE=BIOSIS ABB=ON  PLU=ON  BIOMARKER? OR (BIOLOGICAL OR
                 TUMOR OR NEOPLASM OR CARCINOGEN) (1A) MARKER
L57        59927 SEA FILE=BIOSIS ABB=ON  PLU=ON  IMMUNOASSAY
L59       993700 SEA FILE=BIOSIS ABB=ON  PLU=ON  DIAGNOS?
L60            6 SEA FILE=BIOSIS ABB=ON  PLU=ON  L55 AND L56
L63            6 SEA FILE=BIOSIS ABB=ON  PLU=ON  L55 AND L57
L64            8 SEA FILE=BIOSIS ABB=ON  PLU=ON  L55 AND L59 AND L59
L65            6 SEA FILE=BIOSIS ABB=ON  PLU=ON  L64 NOT (L60 OR L63)

=> s (l60 or l63 or l65) not l62   L62 = inventors, previously displayed
L85           14 (L60 OR L63 OR L65) NOT L62

=> => file wpid; d que l73; d que l74; d que l76; d que l78; d que l80
FILE 'WPIDS' ENTERED AT 17:58:22 ON 02 MAR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE LAST UPDATED:          2 MAR 2004      <20040302/UP>
MOST RECENT DERWENT UPDATE:     200415        <200415/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM
    DERWENT UPDATE 200403.
    THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
    SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
    FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<
```

```
L67          67 SEA FILE=WPIDS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                MK
L69         511 SEA FILE=WPIDS ABB=ON  PLU=ON  BIOMARKER? OR (BIOLOGICAL OR
                TUMOR OR NEOPLASM OR CARCINOGEN) (1A) MARKER
L73           1 SEA FILE=WPIDS ABB=ON  PLU=ON  L67 AND L69


L67          67 SEA FILE=WPIDS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                MK
L70        9297 SEA FILE=WPIDS ABB=ON  PLU=ON  IMMUNOASSAY?
L74           0 SEA FILE=WPIDS ABB=ON  PLU=ON  L67 AND L70


L67          67 SEA FILE=WPIDS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                MK
L71      104587 SEA FILE=WPIDS ABB=ON  PLU=ON  DIAGNOS?
L76           1 SEA FILE=WPIDS ABB=ON  PLU=ON  L67 AND L71 AND HEPATO?/TI


L67          67 SEA FILE=WPIDS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                MK
L77       24237 SEA FILE=WPIDS ABB=ON  PLU=ON  URIN?
L78           1 SEA FILE=WPIDS ABB=ON  PLU=ON  L67 AND L77


L67          67 SEA FILE=WPIDS ABB=ON  PLU=ON  MIDKINE OR MDK PROTEIN OR GENE
                MK
L72       86414 SEA FILE=WPIDS ABB=ON  PLU=ON  CANCER? OR NEOPL? OR CARCINO?
                OR TUMOR? OR TUMOUR?
L79          37 SEA FILE=WPIDS ABB=ON  PLU=ON  L67 AND L72
L80           7 SEA FILE=WPIDS ABB=ON  PLU=ON  L79 AND (HEPATO? OR COLORECT?
                OR NEOANG? OR EARLY OR MONOCLON? OR BINDING)/TI

=> s (l73 or l76 or l78 or l80) not l61
            81 MURAMATSU A?/AU
           793 OKAMOTO K?/AU
           227 ODA M?/AU
            32 KUMAI H?/AU
            12 IKEMATSU S?/AU
           132 SAKUMA S?/AU
L86           6 (L73 OR L76 OR L78 OR L80) NOT L61

=> dup rem l83 l82 l84 l85 l86
FILE 'MEDLINE' ENTERED AT 17:59:10 ON 02 MAR 2004

FILE 'HCAPLUS' ENTERED AT 17:59:10 ON 02 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 17:59:10 ON 02 MAR 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.
```

L61 = inventors, previously displayed

```
FILE 'BIOSIS' ENTERED AT 17:59:10 ON 02 MAR 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'WPIDS' ENTERED AT 17:59:10 ON 02 MAR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT
PROCESSING COMPLETED FOR L83
PROCESSING COMPLETED FOR L82
PROCESSING COMPLETED FOR L84
PROCESSING COMPLETED FOR L85
PROCESSING COMPLETED FOR L86
L87           38 DUP REM L83 L82 L84 L85 L86 (16 DUPLICATES REMOVED)
                 ANSWERS '1-10' FROM FILE MEDLINE
                 ANSWERS '11-26' FROM FILE HCAPLUS
                 ANSWERS '27-33' FROM FILE BIOSIS
                 ANSWERS '34-38' FROM FILE WPIDS

=> d ibib ab ed l87 1-38

L87  ANSWER 1 OF 38     MEDLINE on STN                    DUPLICATE 2
ACCESSION NUMBER:    2003314002     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 12841873
TITLE:               Preoperative serum midkine concentration is a prognostic
                     marker for esophageal squamous cell carcinoma.
AUTHOR:              Shimada Hideaki; Nabeya Yoshihiro; Tagawa Masatoshi;
                     Okazumi Shin-ichi; Matsubara Hisahiro; Kadomatsu Kenji;
                     Muramatsu Takashi; Ikematsu Shinya; Sakuma Sadatoshi;
                     Ochiai Takenori
CORPORATE SOURCE:    Department of Academic Surgery, Graduate School of
                     Medicine, Chiba University, Chuo-ku, Chiba 260-8677,
                     Japan.. hshimada@med.m.chiba-u.ac.jp
SOURCE:              Cancer science, (2003 Jul) 94 (7) 628-32.
                     Journal code: 101168776. ISSN: 1347-9032.
PUB. COUNTRY:        Japan
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200401
ENTRY DATE:          Entered STN: 20030708
                     Last Updated on STN: 20040107
                     Entered Medline: 20040106
AB   High preoperative serum midkine concentration is associated with poor
     survival in patients with esophageal cancer, even after radical surgery,
     and thus may have prognostic value. Midkine (MK), a heparin-binding
     growth factor, is expressed in numerous cancer tissues, and serum MK
     (S-MK) concentrations are increased in patients with various neoplasms.
     The aim of this study is to evaluate the clinical significance of S-MK in
     patients with esophageal squamous cell cancer (SCC). S-MK was measured by
     enzyme-linked immunosorbent assay in 135 healthy controls, 16 patients
     with benign esophageal disease, and 93 patients with primary esophageal
     SCC before surgery. The serum concentrations of carcinoembryonic antigen
     (CEA), SCC antigen (SCC-Ag), and cytokeratin 19 fragment (CYFRA21-1) were
     also evaluated. All patients with esophageal SCC underwent radical
     esophagectomy. Tumor MK expression was assessed by immunohistochemistry
     in 14 fresh tumor specimens. To determine whether S-MK is of value as a
     prognostic factor, the authors conducted a survival analysis using Cox's
     proportional hazards model. S-MK values in patients with esophageal SCC
     were significantly higher than those in healthy controls (417 +/- 342
     pg/ml vs. 154 +/- 76 pg/ml, P < 0.001). Using 300 pg/ml as the cut-off
     value (representing the mean + 2 standard deviations of the S-MK of
```

healthy controls), 61% of patients with esophageal SCC were classified as positive. MK expression by the tumor was significantly associated with high level of S-MK. High S-MK (>/= 300 pg/ml) was associated with tumor size, immunoreactivity and poor survival. Multivariate analysis indicated that S-MK was an independent prognostic factor. S-MK may be a useful tumor marker for esophageal SCC. Increased preoperative S-MK in patients with esophageal SCC is associated with poor survival.

ED Entered STN: 20030708
Last Updated on STN: 20040107
Entered Medline: 20040106

L87 ANSWER 2 OF 38 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003069042 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12579281
TITLE: Increased serum midkine concentration as a possible tumor marker in patients with superficial esophageal cancer.
AUTHOR: Shimada Hideaki; Nabeya Yoshihiro; Okazumi Shin-ichi; Matsubara Hisahiro; Kadomatsu Kenji; Muramatsu Takashi; Ikematsu Shinya; Sakuma Sadatoshi; Ochiai Takenori
CORPORATE SOURCE: Department of Academic Surgery, Graduate School of Medicine, Chiba University, Chiba 260-8677, Japan.. hshimada@med.m.chiba-u.ac.jp
SOURCE: Oncology reports, (2003 Mar-Apr) 10 (2) 411-4. Journal code: 9422756. ISSN: 1021-335X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030212
Last Updated on STN: 20030730
Entered Medline: 20030729

AB Midkine, a heparin-binding growth factor, is expressed in numerous cancer tissues and is reportedly elevated in patients with various neoplasms. The aim of this study was to evaluate the clinicopathological significance of serum midkine concentration (S-MK) in patients with superficial esophageal squamous cell carcinoma (SCC). Pretreatment S-MK was measured by enzyme-linked immunosorbent assay in 135 healthy controls, 16 patients with benign esophageal disease, and 60 patients with primary superficial esophageal squamous cell cancer (SESCC). All patients with SESCC underwent curative resection. The disease was staged according to TNM/UICC guidelines. Serum concentrations of carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), and cytokeratin 19 fragment (CYFRA21-1) were also evaluated in the same populations. S-MK in patients with SESCC (388+/-411 pg/ml) was significantly higher than in benign esophageal disease or healthy controls (183+/-73 and 154+/-76 pg/ml, respectively). Using the mean + 2 standard deviations of healthy control S-MK (300 pg/ml) as the cut-off level, 50% of patients with esophageal SESCC were deemed positive. This S-MK positivity rate for detecting SESCC was significantly higher than for other tumor markers. Thus, S-MK may be useful as a tumor marker to detect SESCC.

ED Entered STN: 20030212
Last Updated on STN: 20030730
Entered Medline: 20030729

L87 ANSWER 3 OF 38 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001014018 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10902971
TITLE: Increased midkine expression in intrahepatic cholangiocarcinoma: immunohistochemical and in situ

hybridization analyses.
AUTHOR: Kato M; Shinozawa T; Kato S; Endo K; Terada T
CORPORATE SOURCE: The Second Department of Pathology, Faculty of Medicine, Tottori University, Yonago, Japan.
SOURCE: Liver, (2000 Jun) 20 (3) 216-21.
Journal code: 8200939. ISSN: 0106-9543.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001102

AB AIMS/BACKGROUND: Midkine (MK) is a novel heparin-binding growth factor whose gene was identified in embryonal carcinoma cells in the early stages of retinoic acid-induced differentiation. This study investigates the overexpression of MK in intrahepatic cholangiocarcinoma (CC). METHODS: Forty-five primary CC specimens from patients (aged 19-81 years, 24 males and 21 females) were examined. Histologically, 17 cases of CC were classified as the well-differentiated type, 19 as moderately-differentiated and 9 as poorly-differentiated. Immunohistochemical analysis was performed using a rat IgG2a monoclonal antibody against the carboxyl terminal region of human MK. RESULTS: We successfully applied this monoclonal antibody against MK to analyze archival paraffin sections. The cancer tissues showed a positive reaction to this antibody, and there was an intense reaction in their cytoplasm. Approximately 40% of individuals with CC (17/45) had tumor cells that expressed MK, and these were classified into the following types: moderately-differentiated type (9/19), well-differentiated type (8/17) and poorly-differentiated type (0/9). In situ hybridization analysis revealed that signals of MK transcripts were found in the cytoplasm of the cancer cells; the distribution and localization of the MK-transcript signals determined by in situ hybridization analysis were similar to those obtained by immunohistochemical analysis. CONCLUSIONS: These findings revealed that CC express increased MK at the messenger RNA and protein levels.

ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001102

L87 ANSWER 4 OF 38 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000091629 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10626184
TITLE: Expression of the midkine gene in human hepatocellular carcinomas.
AUTHOR: Koide N; Hada H; Shinji T; Ujike K; Hirasaki S; Yumoto Y; Hanafusa T; Kadomatsu K; Muramatsu H; Muramatsu T; Tsuji T
CORPORATE SOURCE: First Department of Internal Medicine, Okayama University School of Medicine, Japan.. koide@hospital.okayama-u.ac.jp
SOURCE: Hepato-gastroenterology, (1999 Nov-Dec) 46 (30) 3189-96.
Journal code: 8007849. ISSN: 0172-6390.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

AB BACKGROUND/AIMS: Aberrant expression of Midkine (MK) has been found in

various human carcinomas including hepatocellular carcinoma (HCC). The aim of study is to identify the incidence of MK expression in tumor and surrounding non-tumor tissues of the liver, and to find the correlation of MK expression with other tumor markers. METHODOLOGY: Liver tissues were obtained from 16 patients with HCC and 4 with metastatic liver cancer. Background diseases of the HCC patients include liver cirrhosis and chronic hepatitis of type B or C. RNA was prepared from both cancerous and surrounding non-cancerous tissues, and analyzed for the presence of MK mRNA by RT-PCR, PCR-Southern blot, and Northern blot analysis. RESULTS: MK expression was detected in 12 (75%) of 16 HCCs by PCR-Southern blot analysis, the most sensitive of the 3 methods. Three of 9 surrounding cirrhotic tissues were weakly positive for MK expression, and none of chronic hepatitis and 4 normal tissues were negative. No significant difference was found in clinical and pathological parameters between MK negative and positive cases. Among metastatic cancers, 1 of gastric origin was positive for MK expression, but 1 each of chorangiocellular, gall bladder, and gastrinoma origin was negative. CONCLUSIONS: These results suggest that MK is expressed in the majority of HCC tissues and rarely in surrounding tissues in chronic liver diseases.

ED Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

L87 ANSWER 5 OF 38 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1998379886 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9716029
TITLE: Truncated midkine as a marker of diagnosis and detection of nodal metastases in gastrointestinal carcinomas.
AUTHOR: Aridome K; Takao S; Kaname T; Kadomatsu K; Natsugoe S; Kijima F; Aikou T; Muramatsu T
CORPORATE SOURCE: First Department of Surgery, Kagoshima University Faculty of Medicine, Japan.
SOURCE: British journal of cancer, (1998 Aug) 78 (4) 472-7. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980904

AB Midkine (MK) is a growth factor identified as a product of a retinoic acid-responsive gene. A truncated form of MK mRNA, which lacks a sequence encoding the N-terminally located domain, was recently found in cancer cells. We investigated the expression of the truncated MK mRNA in specimens of 47 surgically removed human gastrointestinal organs using polymerase chain reaction. Truncated MK was not detected in all of the 46 corresponding non-cancerous regions. On the other hand, this short MK mRNA was expressed in the primary tumours in 12 of 16 gastric cancers, 8 of 13 colorectal carcinomas, five of nine hepatocellular carcinomas, two of two oesophageal carcinomas and one ampullary duodenal cancer. In addition, truncated MK was detectable in all of the 14 lymph node metastases but in none of three metastatic sites in the liver, suggesting that truncated MK mRNA could become a good marker of nodal metastases in gastrointestinal tract.

ED Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980904

L87 ANSWER 6 OF 38 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 96425003 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8827454
TITLE: Enzyme-linked immunoassay for midkine, and its application to evaluation of midkine levels in developing mouse brain and sera from patients with hepatocellular carcinomas.
AUTHOR: Muramatsu H; Song X J; Koide N; Hada H; Tsuji T; Kadomatsu K; Inui T; Kimura T; Sakakibara S; Muramatsu T
CORPORATE SOURCE: Department of Biochemistry, Nagoya University School of Medicine.
SOURCE: Journal of biochemistry, (1996 Jun) 119 (6) 1171-5. Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961217

AB Midkine (MK) is a growth factor that promotes neurite outgrowth and survival of neurons, and enhances the plasminogen activator in endothelial cells. A highly sensitive enzyme-linked immunoassay for MK was developed, involving affinity-purified anti-MK antibodies, their biotinylated form, and avidin-beta-galactosidase. The amount of bound avidin-beta-galactosidase was determined using a fluorogenic substrate, 4-methylumbelliferyl-beta-D-galactoside. This method allowed the detection of human and mouse MK in the range of 50 pg-10 ng. Pleiotrophin, which is related to MK in its amino acid sequence, did not show any cross reactivity. Employing this method, the MK levels in the developing mouse brain were determined. The MK level was 2 micrograms/g of wet tissue on the 12th day of gestation, and then steadily decreased during embryogenesis and postnatal development to 30 ng/g two months after birth. The assay method can also be applied to serum samples. Although the MK levels in the sera of normal human subjects were low or undetectable, 0.6-8 ng/ml of MK was detected in samples in the majority of cases of hepatocellular carcinomas.
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961217

L87 ANSWER 7 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003389627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12926063
TITLE: Regulatory regions of growth-related genes can activate an exogenous gene of the alpha-fetoprotein promoter to a comparable degree in human hepatocellular carcinoma cells.
AUTHOR: Tomizawa Minoru; Saisho Hiromitsu; Tagawa Masatoshi
CORPORATE SOURCE: Division of Pathology, Chiba Cancer Center Research Institute, Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, Chuo-ku, Chiba, Japan.. nihminorcib@umin.ac.jp
SOURCE: Anticancer research, (2003 Jul-Aug) 23 (4) 3273-7. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030821

Last Updated on STN: 20031001
Entered Medline: 20030930

AB We examined the transcriptional activation by the regulatory regions of the midkine (MK), survivin (SUR), cyclooxygenase-2 (COX-2), telomerase reverse transcriptase (TERT) and alpha-fetoprotein (AFP) genes in human hepatocellular carcinoma cells. Luciferase assays showed that the SUR regulatory region exhibited the greatest activity and that the MK regulatory region activated the reporter gene better than the enhancer-linked AFP promoter even in high-AFP-producing cells. The COX-2 and TERT regulatory regions also activated the reporter gene better than the AFP enhancer/promoter in intermediate-AFP-producing cells. Combination of the regulatory regions arranged in tandem modulated their transcriptional activities, depending on the arrangement of the promoters and cells examined. These data suggested that the regulatory regions of the growth-related genes could be useful to activate a therapeutic gene in hepatocellular carcinoma cells irrespective of the amounts of AFP production but combinatory use of the promoter regions could not always contribute to enhanced activity.

ED Entered STN: 20030821
Last Updated on STN: 20031001
Entered Medline: 20030930

L87 ANSWER 8 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003424709 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12966430
TITLE: A promoter region of the midkine gene that is frequently expressed in human hepatocellular carcinoma can activate a suicide gene as effectively as the alpha-fetoprotein promoter.
AUTHOR: Tomizawa M; Yu L; Wada A; Tamaoki T; Kadomatsu K; Muramatsu T; Matsubara S; Watanabe K; Ebara M; Saisho H; Sakiyama S; Tagawa M
CORPORATE SOURCE: Division of Pathology, Chiba Cancer Center, 666-2, Nitona, Chuo-ku, Chiba 260-8717, Japan.
SOURCE: British journal of cancer, (2003 Sep 15) 89 (6) 1086-90. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030911
Last Updated on STN: 20031018
Entered Medline: 20031017

AB We examined the expression of the midkine (MK) and alpha-fetoprotein (AFP) genes in 15 paired human specimens obtained from hepatocellular carcinoma (HCC) and the corresponding noncancerous regions of the same patients. A total of 14 HCC but none of the noncancerous specimens were positive for the MK mRNA. In contrast, three HCC specimens and one corresponding noncancerous sample out of the three AFP-positive HCC cases expressed the AFP gene. A 2.3-kb genomic fragment in the regulatory region of the MK gene could activate a fused reporter gene in both AFP-producing and -nonproducing HCC lines, and the MK fragment-mediated transcriptional activity was comparable to the AFP enhancer-linked AFP promoter in AFP-producing cell lines. The AFP-producing but not AFP-nonproducing HCC cell lines that were transfected with the MK promoter-linked herpes simplex virus-thymidine kinase (HSV-TK) gene became susceptible to a prodrug ganciclovir to a similar degree of the HCC transfected with the enhancer-linked AFP promoter-fused HSV-TK gene. These data suggest that the MK promoter can activate a therapeutic gene preferentially in HCC and

is as useful as the AFP promoter in clinical settings.
ED Entered STN: 20030911
Last Updated on STN: 20031018
Entered Medline: 20031017

L87 ANSWER 9 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2002240077 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11977631
TITLE: Correlation between midkine protein overexpression and intrahepatic metastasis in hepatocellular carcinoma.
AUTHOR: Yin Zhengfeng; Luo Xiangji; Kang Xiaoyan; Wu Zongdi; Qian Haihua; Wu Mengchao
CORPORATE SOURCE: Molecular Oncology Research Laboratory, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 200438, China.
SOURCE: Zhonghua zhong liu za zhi [Chinese journal of oncology], (2002 Jan) 24 (1) 27-9.
Journal code: 7910681. ISSN: 0253-3766.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020430
Last Updated on STN: 20020516
Entered Medline: 20020515
AB OBJECTIVE: To investigate the correlation between midkine (MK) protein expression with local infiltration and metastasis in human hepatocellular carcinoma (HCC). METHODS: Immunohistochemical and Western Blot analysis for MK were performed on samples of tumor tissue and the paratumor tissue from HCC and benign liver tumors. RESULTS: The overexpression of MK protein determined by immunohistochemical analysis was similar to that by Western Blot analysis. No specific positivity was detected in either benign liver tumor tissue or normal liver tissue, but most of HCC tissue showed a positive reaction to MK immunostain. No correlation between MK expression and other clinicopathological features in MK negative or positive HCC cases was found. Yet, the overexpression rate of MK protein in HCC with intra-hepatic metastasis was significantly higher than that in HCC without intra-hepatic metastasis. CONCLUSION: In human hepatocellular carcinoma, MK overexpressed at protein level may very well be closely related to local infiltration and metastasis.
ED Entered STN: 20020430
Last Updated on STN: 20020516
Entered Medline: 20020515

L87 ANSWER 10 OF 38 MEDLINE on STN
ACCESSION NUMBER: 1999335197 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10408712
TITLE: Expression of midkine in the early stage of carcinogenesis in human colorectal cancer.
AUTHOR: Ye C; Qi M; Fan Q W; Ito K; Akiyama S; Kasai Y; Matsuyama M; Muramatsu T; Kadomatsu K
CORPORATE SOURCE: Department of Pathology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan.
SOURCE: British journal of cancer, (1999 Jan) 79 (1) 179-84.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990729

AB It has been suggested that a heparin-binding growth factor, midkine (MK), plays an important role in carcinogenesis because of its frequent overexpression in various malignant tumours. To clarify whether or not MK contributes to the early stage of carcinogenesis, we examined the status of MK mRNA in 20 adenomas with moderate- and severe-grade dysplasia, 28 carcinomas and 28 corresponding normal tissues, by means of Northern blotting. The MK expression level was significantly more elevated in adenomas than in normal tissues ($P < 0.001$, unpaired Student's t-test). A difference was also observed between carcinomas and the corresponding normal tissues ($P < 0.04$, paired Student's t-test). Moreover, MK immunostaining was positive in the adenomas with moderate- and severe-grade dysplasia and in the carcinomas, but not in mild-grade dysplasia or in normal tissues. These findings were in line with those on Western blotting. In three patients with both adenomas with moderate- or severe-grade dysplasia and carcinomas, elevated MK expression was observed in the neoplastic lesions. This is the first report of the association of elevated MK expression with the early stage of carcinogenesis in humans.

ED Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990729

L87 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:626612 HCAPLUS
Correction of: 2003:472599
DOCUMENT NUMBER: 139:129181
Correction of: 139:48232
TITLE: Differentially expressed genes for identification, assessment, prevention, and therapy of colon cancer
INVENTOR(S): Berger, Allison; Guillemette, Tracy L.; Schlegel, Robert; Monahan, John E.; Kamatkar, Shubhangi; Thibodeau, Stephen; Burgart, Lawrence J.
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003050243	A2	20030619	WO 2002-US37431	20021121
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003148410	A1	20030807	US 2002-301822	20021121

PRIORITY APPLN. INFO.: US 2001-339971P P 20011210
US 2002-361978P P 20020305

US 2002-381988P P 20020520

AB The invention relates to newly discovered nucleic mols. and proteins that are up-regulated in colon cancer. The 114 markers were identified by transcriptional profiling with RNA derived from 21 normal colon samples, 4 adenomatous polyps, and 25 colon cancer samples using nylon arrays of 44,200 clones, including 30,000 IMAGE clones, 14,000 clones from cDNA libraries generated at Millennium Pharmaceuticals, Inc., and 200 control genes. Higher than normal levels of expression of any of these markers or combination of these markers correlates with the presence of colon cancer. Thus, compns., kits, and methods for detecting, characterizing, preventing, and treating human colon cancers are provided. The present invention claims a total of 228 sequences, but the Sequence Listing was not made available on publication of the patent application.

ED Entered STN: 15 Aug 2003

L87 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2002:341307 HCAPLUS
DOCUMENT NUMBER: 136:368453
TITLE: Preparation of **monoclonal** antibody specific to truncated midkine and the use of antibody for detection of **tumor** cells
INVENTOR(S): Mitsumoto, Tomohiro; Shinozawa, Takao
PATENT ASSIGNEE(S): Denka Seiken Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002125666	A2	20020508	JP 2000-330325	20001030

PRIORITY APPLN. INFO.: JP 2000-330325 20001030

AB This invention provides a process for preparation of monoclonal antibody specific to truncated midkine (tMK). The antibody can be used for detection of human **tumor** cells where the tMK highly expressed.

ED Entered STN: 08 May 2002

L87 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8

ACCESSION NUMBER: 1997:772168 HCAPLUS
DOCUMENT NUMBER: 128:70866
TITLE: The serum level of midkine, a heparin-binding growth factor, as a tumor marker
AUTHOR(S): Song, Xiao-Jun; Muramatsu, Hisako; Aridome, Kuniaki; Aikou, Takashi; Koide, Norio; Tsuji, Takao; Muramatsu, Takashi
CORPORATE SOURCE: Department of Biochemistry, Nagoya University School of Medicine, Nagoya, 466, Japan
SOURCE: Biomedical Research (1997), 18(5), 375-381
CODEN: BRESD5; ISSN: 0388-6107
PUBLISHER: Biomedical Research Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Midkine (MK) is a heparin-binding growth factor distinct from fibroblast growth factors. Serum levels of MK were determined by enzyme-linked immunoassay using affinity-purified anti-human MK antibody. Elevated levels of MK were frequently observed in sera from patients with various carcinomas including lung carcinoma, bile duct carcinoma, colon carcinoma and esophageal carcinoma. Most patients with lung carcinoma showed high

MK serum values. In colorectal carcinoma, some correlation was observed between high MK value and tumor invasion. Surgical removal of carcinomas invariably resulted in decreases in the MK level. Determination of serum MK may be useful as an aid in initial screening of certain carcinomas, such as lung carcinoma.
ED Entered STN: 11 Dec 1997
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1998:155879 HCAPLUS
DOCUMENT NUMBER: 128:229025
TITLE: Growth factors and prostate **tumors**
AUTHOR(S): Cussenot, O.
CORPORATE SOURCE: Service Urologie, Hopital St. Louis, Paris, 75010, Fr.
SOURCE: Annales d'Endocrinologie (1997), 58(5), 370-380
CODEN: ANENAG; ISSN: 0003-4266
PUBLISHER: Masson Editeur
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French
AB A review, with 66 refs. Prostate growth factor (PGF) was the first growth factor isolated from the prostate. Because of its proliferative effect on fibroblasts and its affinity for heparin, it was first recognized as belonging to the family of fibroblastic growth factors then identified as bFGF (basic fibroblast growth factor) by Story in 1980. The presence of paracrine signals between the fibromuscular stroma and the epithelial tissue in the prostate were first demonstrated in 1970 by the incapacity of epithelial cells to grow without the presence of mesenchymal tissue. These paracrine relations are established during embryogenesis of the prostate and are required for its development and functional control in the adult. Keratinocyte growth factor (KGF), also called FGF-7, could be a stomal androgen mediator with a mitogenic paracrine effect on he epithelium. Dysregulation of growth factors has been suggested to be involved in the development of prostate **tumors** in elderly men (benign hypertrophy and **cancer** of the prostate). FGFs probably play an important role in benign prostate and hypertrophy. Several studies have demonstrated an important rise in mRNA levels for these factors in benign hyperplastic tissue compared with "normal" tissue. This increased level would be associated with fibromuscular proliferation in periglandular tissue and could explain, at least in part, the epithelial hyperplasia often associated with the paracrine stimulating effect. In prostate **cancer**, different families of growth factors have been associated with acquisition in aggressive **tumor** functions. The EGF receptor and its ligands, the IGF family, TGFβa and certain neuropeptides could be partially implicated in androgen-independent autocrine growth. Heparin-related growth factors (FGFs, Midkine family), VEGF or endothelin could be more particularly implicated in metastatic progression by stimulating cell motility, angiogenesis and metastatic implantation by a two-way cooperation between the **tumor** and the stroma in which it is implanted. Several of these factors are found in the blood stream and have been proposed as **biol. markers** of poor prognosis. Knowledge of peptides regulating prostate growth or of growth factor antagonists has led to the concept of antipeptidergic therapy as an adjuvant in antiprostate **tumor** regiments.
ED Entered STN: 16 Mar 1998
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:8538 HCAPLUS

DOCUMENT NUMBER: 140:126272
TITLE: Highly specific marker genes for detecting minimal gastric cancer cells in cytology negative peritoneal washings
AUTHOR(S): Mori, Kazuhiko; Aoyagi, Kazuhiko; Ueda, Tetsuya; Danjoh, Inaho; Tsubosa, Yasuhiro; Yanagihara, Kazuyoshi; Matsuno, Yoshihiro; Sasako, Mitsuru; Sakamoto, Hiromi; Mafune, Ken-ichi; Kaminishi, Michio; Yoshida, Teruhiko; Terada, Masaaki; Sasaki, Hiroki
CORPORATE SOURCE: Genetics Division, National Cancer Center Research Institute, Tokyo, 104-0045, Japan
SOURCE: Biochemical and Biophysical Research Communications (2004), 313(4), 931-937
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peritoneal wash cytol. plays a pivotal role in the decision for gastric cancer treatment because advanced gastric cancer often turns out incurable with peritoneal metastasis. Mol. detection of minimal cancer cells from peritoneal washings may overcome the sensitivity boundary of conventional cytol. and contribute to the prediction of the disease outcome. To select marker candidates out of ten thousands of genes, we performed microarray analyses in 12 gastric cell lines and 8 peritoneal washings of early stage cases. With 40 candidates selected by the above expression profiling, RT-PCR in 16 representative peritoneal wash samples was performed to identify genes specific to cytol. pos. samples. The finally selected five genes, CK20, FABP1, MUC2, TFF1, and TFF2, were then evaluated for their utility as a marker for minimal residual disease in 99 peritoneal wash samples. Nested RT-PCR using the five genes showed pos. results highly specific to incurable cases (91-100%). With a high specificity, the combination of these five genes succeeded in identifying 6 out of 20 (30%) addnl. patients with all types of early recurrence that could not be predicted by the conventional method. The six newly identified recurrences included four non-peritoneal ones, showing that RT-PCR using the five genes without a real-time quant. PCR technique contributes to the detection of minimal residual disease.

ED Entered STN: 07 Jan 2004
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:511070 HCAPLUS
DOCUMENT NUMBER: 139:64450
TITLE: Prostate cancer diagnosis and outcome prediction by gene expression analysis
INVENTOR(S): Golub, Todd R.; Febbo, Phillip G.; Ross, Kenneth N.; Sellers, William R.
PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, USA; Dana-Farber Cancer Institute, Inc.
SOURCE: PCT Int. Appl., 151 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053223	A2	20030703	WO 2002-US41209	20021220

WO 2003053223 A3 20030904
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003152980 A1 20030814 US 2002-325457 20021219
PRIORITY APPLN. INFO.: US 2001-343448P P 20011221

AB Methods identifying prostate cancer, methods for prognosing and diagnosing prostate cancer, methods for identifying a compound that modulates prostate cancer development, methods for determining the efficacy of a prostate cancer therapy, and oligonucleotide microarrays containing probes for genes involved in prostate cancer development are described. High-quality oligonucleotide-based expression data was obtained from 52 prostate tumors and 50 prostate samples lacking detectable tumor using Affymetrix human 95v microarrays containing 12,600 total features for genes, ESTs, and controls. In particular, a 5-gene model of prostate cancer outcome prediction is provided based on platelet-derived growth factor receptor β, chromogranin A, and HOXC6 (which show increased expression in recurrent tumors), while inositol triphosphate receptor type 3, and β-galactoside sialotransferase show decreased expression in recurrent tumors.

ED Entered STN: 04 Jul 2003

L87 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:298431 HCAPLUS
DOCUMENT NUMBER: 139:34235
TITLE: Identification of Cervical Cancer Markers by cDNA and Tissue Microarrays
AUTHOR(S): Chen, Yan; Miller, Christine; Mosher, Rebecca; Zhao, Xumei; Deeds, Jim; Morrissey, Mike; Bryant, Barb; Yang, David; Meyer, Ron; Cronin, Frank; Gostout, Bobbie S.; Smith-McCune, Karen; Schlegel, Robert
CORPORATE SOURCE: Departments of Molecular and Cell Biology, Millennium Pharmaceuticals, Inc., Cambridge, MA, 02139, USA
SOURCE: Cancer Research (2003), 63(8), 1927-1935
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Pap test has effectively reduced the incidence and mortality of cervical cancer. However, because of the morphol. basis of this test, sensitivity and specificity are less than ideal, a situation that complicates the clin. management of women diagnosed with low-grade cervical abnormalities. In an attempt to understand the mol. basis of cervical tumorigenesis and to discover mol. markers for accurate cervical cancer screening, we used cDNA microarrays containing >30,000 Unigene clones to examine the gene expression patterns of 34 cervical tissues from different clin. defined stages. It was found that global gene expression patterns separated normal cervical tissues and low-grade squamous intraepithelial lesions from cervical cancers and most of the high-grade squamous intraepithelial lesions (HSILs). Among the top 62 genes/(expressed sequence tags) that were overexpressed in tumors and HSIL tissues, 35 were confirmed using in situ hybridization on cervical tissue

microarrays. Many of these genes were overexpressed in high-grade dysplastic and malignant cervical epithelium or in stroma adjacent to the diseased tissues, with cellular proliferation and extracellular matrix-associated genes being the most common. In general, the extent of gene overexpression increased as the lesions progressed from low-grade squamous intraepithelial lesions to HSILs and finally to cancer. It is hoped that with addnl. development, some of these markers will improve the interpretation of cervical screening tests and provide useful information for patient management decisions.

ED Entered STN: 18 Apr 2003

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:403452 HCAPLUS

DOCUMENT NUMBER: 139:211763

TITLE: Correlation of elevated level of blood midkine with poor prognostic factors of human neuroblastomas

AUTHOR(S): Ikematsu, S.; Nakagawara, A.; Nakamura, Y.; Sakuma, S.; Wakai, K.; Muramatsu, T.; Kadomatsu, K.

CORPORATE SOURCE: Department of Biochemistry, Nagoya University Graduate School of Medicine, Showaku, 466-8550, Japan

SOURCE: British Journal of Cancer (2003), 88(10), 1522-1526
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The heparin-binding growth factor midkine (MK) is the product of a retinoic acid-responsive gene, and is implicated in neuronal survival and differentiation, and carcinogenesis. The authors previously reported that MK mRNA expression is elevated in neuroblastoma specimens at all stages, whereas pleiotrophin, the other member of the MK family, is expressed at high levels in favorable neuroblastomas. As MK is a secretory protein, it can be detected in the blood. Here, the authors show a significant correlation of the plasma MK level with prognostic factors of neuroblastomas. The plasma MK level was determined in 220 patients with neuroblastomas, and compared with that in children without malignant tumors (n=17, <500 pg ml-1). The plasma MK level became significantly elevated with advancing stages (stage 1: 445 pg ml-1 (median), n=73; stage 2: 589, n=39; stage 3: 864, n=40; stage 4: 1445, n=56; and stage 4S: 2439, n=12). More importantly, a higher MK level was strongly correlated with poor prognostic factors: over 1 yr of age (P=0.0299), MYCN amplification (P<0.0001), low TrkA expression (P=0.0005), nonmass screening, sporadic neuroblastomas (P<0.0001), and diploidy/tetraploidy (P=0.0007). Thus, these results demonstrate that the plasma MK level is a good marker for evaluating the progression of neuroblastomas. Moreover, considering the ability of antisense MK oligodeoxyribonucleotide to suppress tumor growth of colorectal carcinoma cells in nude mice, as recently reported, the present study suggests that MK is a possible candidate mol. target for therapy for neuroblastomas.

ED Entered STN: 27 May 2003

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:964539 HCAPLUS

DOCUMENT NUMBER: 138:34222

TITLE: Differentially expressed human genes and their encoded proteins useful for identification, assessment, prevention, and therapy of cervical cancer

INVENTOR(S): Schlegel, Robert; Chen, Yan; Zhao, Xumei; Monahan, John E.; Kamatkar, Shubhangi; Gannavarapu, Manjula; Glatt, Karen; Hoersch, Sebastian
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 386 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002101075	A2	20021219	WO 2002-US18638	20020612
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003087270	A1	20030508	US 2002-171311	20020612

PRIORITY APPLN. INFO.: US 2001-298155P P 20010613
US 2001-298159P P 20010613
US 2001-335936P P 20011114

AB The invention relates to 119 newly discovered nucleic acid mols. and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia in human patients. Cervical tumor-specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I, and 12 normal cervical tissues. The top up-regulated clones in tumors or DIN III cervical tissues, as determined by proprietary statistical anal. methods, were selected, and full-length clones obtained by contiguous assembly of EST sequences. Compns., kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers are provided.
ED Entered STN: 20 Dec 2002

L87 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:888889 HCAPLUS
DOCUMENT NUMBER: 138:1032
TITLE: RT-PCR detection of a human GD2 synthase mRNA and application to cancer diagnosis and detection of cancer stage
INVENTOR(S): Cheung, Irene Y.; Cheung, Nai-Kong V.
PATENT ASSIGNEE(S): Sloan-Kettering Institute for Cancer Research, USA
SOURCE: PCT Int. Appl., 165 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092767	A2	20021121	WO 2002-US15037	20020419
WO 2002092767	A3	20031218		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-290527P P 20010511

AB The present invention provides a method to measure a human GD2 synthase mRNA comprising steps of: (a) obtaining a mRNA sample; (b) performing real-time quant. RT-PCR on the sample using appropriate primers of GD2 synthase; and (c) determining the amount of GD2 synthase mRNA. The invention also provides a method to diagnose a human subject which bears cancer expressing GD2 synthase. Furthermore, this invention provides a method to stage a cancer expressing GD2 synthase in a subject. Finally, this invention provides a kit for detection of GD2 synthase.

ED Entered STN: 22 Nov 2002

L87 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:833060 HCAPLUS
DOCUMENT NUMBER: 137:347543
TITLE: Gene expression profile in human lung cancer and its use in diagnosis and screening for modulators of lung cancer
INVENTOR(S): Aziz, Natasha; Murray, Richard
PATENT ASSIGNEE(S): Eos Biotechnology, Inc., USA
SOURCE: PCT Int. Appl., 453 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 37
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002086443	A2	20021031	WO 2002-US12476	20020418

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2002086443	A2	20021031	WO 2002-XA12476	20020418

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NP, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-284770P P 20010418

	US 2001-290492P	P	20010510
	US 2001-339245P	P	20011109
	US 2001-350666P	P	20011113
	US 2001-334370P	P	20011129
	US 2002-372246P	P	20020412
	WO 2002-US12476	A	20020418

AB The present invention provides nucleotide sequences of genes that are up- and down-regulated in lung cancer cells. Such genes are useful for diagnostic purposes, and also as targets for screening for therapeutic compds. that modulate lung cancer, such as antibodies. The expressed genes are identified using the Eos/Affymetrix Hu03 Genechip array to screen normal lung, various forms of lung cancer, and chronically non-malignant lung diseases such as fibrosis, emphysema, and bronchitis. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

ED Entered STN: 01 Nov 2002

L87 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:276203 HCAPLUS
DOCUMENT NUMBER: 136:290017
TITLE: Gene expression profiles in hepatocellular carcinoma and metastatic liver cancer
INVENTOR(S): Horne, Darci; Alvares, Christopher; Peres da Silva, Supriya; Vockley, Joseph G.
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 298 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002029103	A2	20020411	WO 2001-US30589	20011002
WO 2002029103	A3	20030904		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002142981	A1	20021003	US 2001-880107	20010614
AU 2002011313	A5	20020415	AU 2002-11313	20011002

PRIORITY APPLN. INFO.:

US 2000-237054P	P	20001002	
US 2000-211379P	P	20000614	
WO 2001-US30589	W	20011002	

AB The present invention identifies the global changes in gene expression associated with liver cancer by examining gene expression in tissue from normal liver, metastatic malignant liver and hepatocellular carcinoma (HCC). Gene signatures were obtained by hybridizing cDNA from liver samples mRNA onto the Affymetrix HuGeneFl array and the Human Hu35k set of arrays. There are 8479 genes and ESTs in the pos. Gene Signature for the HCC tumors, and a total of 23,233 genes and ESTs are included in the neg. Gene Signature of the HCC samples (e.g., all the genes that have been completely turned off during tumorigenesis, as well as those genes that

are not usually expressed in liver tissue). A differential comparison of the genes and ESTs expressed in the normals and the two different types of liver tumors identifies a subset of the genes included in the pos. Gene Signatures that are uniquely expressed in each sample set. A number of the tumor-expressing genes are closely examined to determine if their expression patterns correlate with previous reports published in the literature, and to define a logical relationship between the gene and hepatocarcinogenesis. The present invention also identifies expression profiles which serve as useful diagnostic markers as well as markers that can be used to monitor disease states, disease progression, drug toxicity, drug efficacy and drug metabolism

ED Entered STN: 12 Apr 2002

L87 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:285562 HCAPLUS
DOCUMENT NUMBER: 137:61578
TITLE: Expressed gene sets as markers for specific tumors
INVENTOR(S): Ramaswamy, Sridhar; Golub, Todd B.; Tamayo, Pablo; Angelo, Michael
PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, USA; Dana-Farber Cancer Institute, Inc.
SOURCE: PCT Int. Appl., 715 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024956	A2	20020328	WO 2001-XB29287	20010919
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2002024956	A2	20020328	WO 2001-US29287	20010919
WO 2002024956	C1	20030306		
WO 2002024956	A3	20030626		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:
US 2000-233534P P 20000919
US 2001-278749P P 20010326
WO 2001-US29287 W 20010919

AB Sets of genetic markers for specific tumor classes are described, as well as methods of identifying a biol. sample based on these markers. Total RNA was isolated from .apprx.300 human tumor and normal tissue specimens representing 30 individual classes of tumor or normal tissue, and cDNA produced using established mol. biol. protocols was hybridized to two high

d. Affymetrix oligonucleotide microarrays (Hu6800FL and Hu35KsubA0). Raw expression data was combined into a master data set containing the expression values for between 6800 and 16,000 genes expressed by each individual sample. A filter was applied to this data set which only allows those genes expressed at 3-fold above baseline and with an absolute difference in expression value of 100 to pass. By comparing the sets of genes which are expressed specifically in one class of tumor (e.g., pancreatic adenocarcinoma) vs. its accompanying normal tissue (e.g., normal pancreas), sets of genes were determined which are specific to various tumors and their normal tissue counterparts. Also described are diagnostic, prognostic, and therapeutic screening uses for these markers, as well as oligonucleotide arrays comprising these markers. [This abstract record is one of 4 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].
ED Entered STN: 17 Apr 2002

L87 ANSWER 24 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:686505 HCAPLUS
DOCUMENT NUMBER: 133:265646
TITLE: Antibody and **immunoassay** for detecting midkine in clinical sample
INVENTOR(S): Yano, Akira
PATENT ASSIGNEE(S): Meiji Milk Products, Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000266750	A2	20000929	JP 1999-70734	19990316

PRIORITY APPLN. INFO.: JP 1999-70734 19990316
AB Provided is a highly sensitive method for detecting human midkine in clin. samples using anti-midkine antibody. The immunoassay method is an ELISA performed in a reaction buffer with ionic strength 0.3-1.5, adjusted with salts, e.g. potassium chloride. The method is useful for diagnosis of midkine-related diseases, e.g. tissue repair and nerve extension, **cancer** development, etc.
ED Entered STN: 29 Sep 2000

L87 ANSWER 25 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:699510 HCAPLUS
DOCUMENT NUMBER: 131:320927
TITLE: Immunohistochemical analysis of midkine expression in human prostate carcinoma
AUTHOR(S): Konishi, Noboru; Nakamura, Mitsutoshi; Nakaoka, Shingo; Hiasa, Yoshio; Cho, Masaki; Uemura, Hirotsugu; Hirao, Yoshihiko; Muramatsu, Takashi; Kadomatsu, Kenji
CORPORATE SOURCE: Second Department Pathology, Nara Medical Univ., Kashihara, 634, Japan
SOURCE: Oncology (1999), 57(3), 253-257
CODEN: ONCOBS; ISSN: 0030-2414
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Midkine (MK) is a growth/differentiation factor frequently expressed at high levels in some types of human malignancies. To investigate whether

MK is a useful marker in prostate carcinogenesis, immunohistochem. anal. was performed on samples of both latent and clin. prostate cancers of various stages, as well as on specimens of normal gland and prostatic intraepithelial neoplasia (PIN). Of the 80 clin. cancers examined, 69 specimens (86.3%) were immunoreactive for MK, with metastatic lesions generally showing higher expression than the corresponding primaries; normal prostate tissues were neg. or showed only weak staining. Midkine was also detected in 12 of 15 latent cancers (80%) and in 12 of 16 cases of PIN (75%). In sections of whole prostate, MK showed variable expression through tumorous sections, probably in reflection of heterogeneous cell populations. The results demonstrate the possible value of MK as a marker for early and latent disease, as well as for more advanced clin. stages of prostate cancer.

ED Entered STN: 02 Nov 1999

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 26 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:405514 HCAPLUS

DOCUMENT NUMBER: 129:108007

TITLE: **Sandwich** immunoassay method using polyclonal antibodies from 2 species of animals

INVENTOR(S): Yano, Akira; Yokoyama, Minehiko; Ikematsu, Shinya; Oda, Munehiro; Muramatsu, Takashi; Muramatsu, Sumiko

PATENT ASSIGNEE(S): Meiji Milk Products, Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10160735	A2	19980619	JP 1997-17749	19970116
PRIORITY APPLN. INFO.:			JP 1996-24850	19960119
			JP 1996-281660	19961004

AB Disclosed is a sandwich immunoassay method using 2 polyclonal antibodies prepared in 2 different species of animals immunized with the same antigen, which antibodies recognize 2 different epitopes, resp., on the antigen. Moreover, using 2 different polyclonal antibodies give the sensitivity comparable to that of using monoclonal antibodies. Determination of human midkine (MK) by using the rabbit anti-human MK polyclonal antibody and the chicken anti-human MK polyclonal antibody in a sandwich immunoassay was shown.

ED Entered STN: 02 Jul 1998

L87 ANSWER 27 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:8941 BIOSIS

DOCUMENT NUMBER: PREV200300008941

TITLE: **Midkine** and pleiotrophin: Two related proteins involved in development, survival, inflammation and tumorigenesis.

AUTHOR(S): Muramatsu, Takashi [Reprint Author]

CORPORATE SOURCE: Department of Biochemistry, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, 466-8550, Japan
tmurama@med.nagoya-u.ac.jp

SOURCE: Journal of Biochemistry (Tokyo), (Sep 2002) Vol. 132, No. 3, pp. 359-371. print.
CODEN: JOBIAO. ISSN: 0021-924X.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Dec 2002
Last Updated on STN: 18 Dec 2002

AB **Midkine** (MK) and pleiotrophin (PTN) are low molecular weight proteins with closely related structures. They are mainly composed of two domains held by disulfide bridges, and there are three antiparallel beta-sheets in each domain. MK and PTN promote the growth, survival, and migration of various cells, and play roles in neurogenesis and epithelial mesenchymal interactions during organogenesis. A chondroitin sulfate proteoglycan, protein-tyrosine phosphatase zeta (PTPzeta), is a receptor for MK and PTN. The downstream signaling system includes ERK and PI3 kinase. MK binds to the chondroitin sulfate portion of PTPzeta with high affinity. Among the various chondroitin sulfate structures, the E unit, which has 4,6-disulfated N-acetylgalactosamine, provides the strongest binding site. The expression of MK and PTN is increased in various human tumors, making them promising as **tumor markers** and as targets for tumor therapy. MK and PTN expression also increases upon ischemic injury. MK enhances the migration of inflammatory cells, and is involved in neointima formation and renal injury following ischemia. MK is also interesting from the viewpoints of the treatment of neurodegenerative diseases, increasing the efficiency of in vitro development, and the prevention of HIV infection.

ED Entered STN: 18 Dec 2002
Last Updated on STN: 18 Dec 2002

L87 ANSWER 28 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:195324 BIOSIS
DOCUMENT NUMBER: PREV200200195324
TITLE: **Immunoassay** for measuring the heparin-binding growth factors HARP and MK in biological fluids.
AUTHOR(S): Soulie, Patrick; Heroult, Melanie; Bernard, Isabelle; Kerros, Marie-Emmanuelle; Milhiet, Pierre Emmanuel; Delbe, Jean; Barritault, Denis; Caruelle, Daniele; Courty, Jose [Reprint author]
CORPORATE SOURCE: Laboratoire de Recherche sur la Croissance Cellulaire la Reparation et la Regeneration Tissulaires (CRRET), UPRES-A CNRS 7053, Universite Paris XII, Val de Marne avenue du General de Gaulle, 94010, Creteil, France courty@univ-paris12.fr
SOURCE: Journal of Immunoassay and Immunochemistry, (February, 2002) Vol. 23, No. 1, pp. 33-48. print.
ISSN: 1532-1819.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002

AB Heparin-affin regulatory peptide (HARP) and **Midkine** (MK) belong to a family of growth/differentiation factors that have a high affinity for heparin. The involvement of these molecules in various proliferative diseases prompted us to develop an assay for measuring the concentrations of these factors in biological fluids and culture media. This report describes an **immunoassay** that uses only commercially available materials, based on the high affinity of certain molecules for heparin. It consists of adsorbing heparin-BSA covalent complexes to microtiter plate wells and to quantify the heparin bound HARP or MK by using appropriate antibody. The method is specific and measures concentrations ranging from 40-1200 pg/mL HARP and from 25-1200 pg/mL MK and various parameters are investigated. The within-assay coefficient of variation was less than 5% for both assays. The method was checked by measuring the

concentrations of these growth factors in the sera of healthy humans and in patients with cancer. As previously reported, we confirmed that the serum concentrations of MK are higher in patients with tumours (n = 139) than in controls (n = 19). The synthesis of HARP and MK by various cells in culture was also analysed.
ED Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002

L87 ANSWER 29 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:158808 BIOSIS
DOCUMENT NUMBER: PREV200000158808
TITLE: A malignant rhabdoid tumor of the kidney occurring concurrently with a brain tumor: Report of a case.
AUTHOR(S): Adachi, Yasuo [Reprint author]; Takamatsu, Hideo; Noguchi, Hiroyuki; Tahara, Hiroyuki; Fukushige, Takahiko; Takasaki, Takashi; Yoshida, Aichi; Kamenosono, Akira; Kikuchi, Jiro; Asatani, Masayo; Kawakami, Kiyoshi
CORPORATE SOURCE: Department of Pediatric Surgery, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima, 890-8520, Japan
SOURCE: Surgery Today (Tokyo), (March, 2000) Vol. 30, No. 3, pp. 298-301. print.
ISSN: 0941-1291.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Apr 2000
Last Updated on STN: 4 Jan 2002
AB Malignant rhabdoid tumor of the kidney (MRTK) is one of the most lethal neoplasms to occur in young infants. Cases of MRTK accompanying an embryonal tumor in the central nervous system have occasionally been described. We present herein an interesting case of MRTK that was clinically **diagnosed** preoperatively. A male infant aged 6 months with both a midline brain tumor and a renal neoplasm was transferred to our institution. Although roentgenographic evaluation suggested that the renal lesion was a Wilms' tumor, **midkine** (MK), a growth and differentiation factor characteristically present in the urine of patients with Wilms' tumor, was not detected. A preoperative **diagnosis** of MRTK was established based on the lack of urinary MK in addition to the typical clinical features of the young age and the concurrent brain tumor.
ED Entered STN: 26 Apr 2000
Last Updated on STN: 4 Jan 2002

L87 ANSWER 30 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:355012 BIOSIS
DOCUMENT NUMBER: PREV199800355012
TITLE: Increased serum **midkine** levels during hemodialysis using heparin in chronic renal failure.
AUTHOR(S): Fujisawa, Kazuhiro; Matsumoto, Yoshihiro [Reprint author]; Muramatsu, Hisako; Shinzato, Toru; Hiramatsu, Kenjyu; Horie, Katunori; Cai, Zhe; Oka, Hirohumi; Amano, Izumi; Muramatsu, Takashi; Maeda, Kenji
CORPORATE SOURCE: Dep. Internal Med., Daiko Med. Cent., 1-1-20 Daiko-minami, Higashi-ku, Nagoya 461-0047, Japan
SOURCE: Journal of Biochemistry (Tokyo), (May, 1998) Vol. 123, No. 5, pp. 864-869. print.
CODEN: JOBIAO. ISSN: 0021-924X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 1998
Last Updated on STN: 13 Aug 1998

AB The heparin-binding growth factor **midkine** (MK) has been implicated in neuron growth, angiogenesis, and inflammation. In this study, to-elucidate the involvement of MK in the development of pathologies associated with uremia, we examined the serum MK levels in patients receiving hemodialysis (HD) by a highly sensitive enzyme-linked **immunoassay**. Although no significant difference was found between control serum and serum before dialysis in HD patients, serum MK levels increased significantly at the early stage of HD sessions using heparin and gradually decreased after dialysis. In normal controls, intravenous administration of heparin induced a similar sudden increase of MK, but the subsequent decrease was also rapid. In an in vitro study, MK was released in time- and heparin- dose dependent manner from cultured vessels, but not from peripheral leukocytes. These results indicate that, in HD patients, MK is released mainly from endothelial cells immediately after administration of heparin during HD and disappears gradually from blood due to renal impairment. This phenomenon might affect some complications associated with HD.

ED Entered STN: 13 Aug 1998
Last Updated on STN: 13 Aug 1998

L87 ANSWER 31 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1998:313715 BIOSIS
DOCUMENT NUMBER: PREV199800313715
TITLE: **Midkine**, a new heparin-binding growth/differentiation factor: Expression and distribution during embryogenesis and pathological status.
AUTHOR(S): Sun, Xue-Zhi [Reprint author]; Fukui, Yoshihiro
CORPORATE SOURCE: Dep. Anat., Sch. Med., Univ. Tokushima, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan
SOURCE: Congenital Anomalies, (March, 1998) Vol. 38, No. 1, pp. 25-38. print.
CODEN: CGANE7. ISSN: 0914-3505.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Jul 1998
Last Updated on STN: 22 Jul 1998

AB **Midkine** (MK) is a 13 kDa heparin-binding growth factor found as a product of a retinoic acid-responsive gene. MK is rich in basic amino acids and cysteine and its sequence is not homologous with any other proteins so far reported, so it is a new family of heparin-binding growth factor. It has been found that MK exerts variety of biological activities such as neurite-promoting, neuronal cell survival and differentiation-inducing activities. MK is strictly expressed during the mouse embryogenesis; among the adult organs, it is detected only in the kidney. MK is also strongly expressed in a number of human carcinomas and specifically localized in senile plaques in the brain of patients with Alzheimer disease. More recently, it has been reported that MK is an important molecule regulating inflammation response and tissue repair. These results demonstrated that the relevance of MK not only in normal development, but also in processes leading to tissue repair or diseases. Increased MK gene expression is a common phenomenon observed in many human carcinomas, therefore MK is of significant interest in cancer biology. As a new growth/differentiation factor, many issues including the detailed sites and the precise time of MK expression, the exact cellular source which synthesizes and secretes MK, the signal transducing receptors for MK, the mechanisms underlying those developmentally regulated expression and its potential clinical significance still remain unknown. To elucidate the molecular mechanisms of MK action will lead not only to a deeper understanding of developmental processes, but also to the ultimate

obtaining a key to **diagnose** and treat human carcinomas.
ED Entered STN: 22 Jul 1998
Last Updated on STN: 22 Jul 1998

L87 ANSWER 32 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:279054 BIOSIS
DOCUMENT NUMBER: PREV199799578257
TITLE: **Midkine** is a marker for **diagnosis** of gastrointestinal cancer.
AUTHOR(S): Aridome, K. [Reprint author]; Takao, S. [Reprint author]; Kaname, T.; Kadomatsu, K.; Natsugoe, S. [Reprint author]; Kijima, F. [Reprint author]; Muramatsu, T.; Aikou, T. [Reprint author]
CORPORATE SOURCE: First Dep. Surg., Kagoshima Univ., Kagoshima, Japan
SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A534. Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association. Washington, D.C., USA. May 11-14, 1997. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 1997
Last Updated on STN: 3 Jul 1997
ED Entered STN: 3 Jul 1997
Last Updated on STN: 3 Jul 1997

L87 ANSWER 33 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:253648 BIOSIS
DOCUMENT NUMBER: PREV199395132823
TITLE: A new family of heparin-binding growth/differentiation factors: Increased **midkine** expression in Wilms' tumor and other human carcinomas.
AUTHOR(S): Tsutsui, Jun-Ichiro [Reprint author]; Kadomatsu, Kenji; Matsubara, Shyuichiro; Nakagawara, Akira; Hamanoue, Masahiro; Takao, Sonshin; Shimazu, Hisaaki; Ohi, Yoshitada; Muramatsu, Takashi
CORPORATE SOURCE: Dep. Biochem., Fac. Med., Kagoshima Univ., 8-35-1 Sakuragaoka, Kagoshima 890, Japan
SOURCE: Cancer Research, (1993) Vol. 53, No. 6, pp. 1281-1285. CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 May 1993
Last Updated on STN: 21 May 1993
AB **Midkine** (MK) and heparin-binding growth-associated molecule/pleiotrophin form a new family of heparin-binding growth/differentiation factors. We studied MK gene expression in human tumors. In normal human reference tissues, MK was highly expressed in the mucosal tissue of the small intestine, moderately in the thyroid, weakly in the tissues of the lung, colon, stomach, kidney, and spleen, and not at all in the liver. All of 6 surgically removed specimens of Wilms' tumor highly expressed MK. Also, a moderate to intense level of MK expression was noted in the majority of surgically removed hepatocellular carcinomas. The MK mRNA level was analyzed in a number of cultured and nude mice-transplanted lines of human tumors. In stomach, colon, pancreatic, lung, and esophageal carcinomas, a moderate to high level of MK expression was found in the majority of them. These results suggest an important role of MK in the development and/or biological behavior of tumors and raised a possibility to use MK as a **diagnostic** marker.

Heparin-binding growth associated molecule/pleiotrophin mRNA was low or scarcely detectable in samples analyzed thus far except for significant levels of the expression that were observed in PA-1 teratocarcinoma cells and in some surgical specimens of Wilms' tumor.
ED Entered STN: 21 May 1993
Last Updated on STN: 21 May 1993

L87 ANSWER 34 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2004-142995 [14] WPIDS
DOC. NO. NON-CPI: N2004-113997
DOC. NO. CPI: C2004-057598
TITLE: Use of **tumor** endothelial **marker** proteins for inhibiting **neoangiogenesis**, screening for **neoangiogenesis**, promoting **neoangiogenesis**, identifying candidate drugs for treating **tumors** or promoting wound healing.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): KINZLER, K W; ST CROIX, B; VOGELSTEIN, B
PATENT ASSIGNEE(S): (UYJO) UNIV JOHNS HOPKINS
COUNTRY COUNT: 105
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004005883	A2	20040115	(200414)*	EN	113

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004005883	A2	WO 2003-US16250	20030702

PRIORITY APPLN. INFO: US 2003-458964P 20030401; US 2002-393023P 20020702
AB WO2004005883 A UPAB: 20040226
NOVELTY - Use of **tumor** endothelial **marker** (TEM) proteins for identifying a ligand involved in endothelial cell regulation, inhibiting neoangiogenesis, screening for neoangiogenesis, promoting neoangiogenesis, identifying candidate drugs for treating **tumors** or promoting wound healing or identifying endothelial cells, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) identification of a ligand involved in endothelial cell regulation;
(2) inhibiting neoangiogenesis;
(3) promoting neoangiogenesis in a patient;
(4) screening for neoangiogenesis in a patient;
(5) identify candidate drugs for treating **tumors** or promoting wound healing; and
(6) identifying endothelial cells.
ACTIVITY - Cytostatic; Vulnerary. No biological data given.
MECHANISM OF ACTION - None given.
USE - The **tumor** endothelial **marker** (TEM) proteins

are useful for identifying a ligand involved in endothelial cell regulation, inhibiting neoangiogenesis, screening for neoangiogenesis, promoting neoangiogenesis, identifying candidate drugs for treating **tumors** or promoting wound healing or identifying endothelial cells (claimed).
Dwg.0/0
ED 20040226

L87 ANSWER 35 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-248087 [24] WPIDS
CROSS REFERENCE: 2004-143953 [14]
DOC. NO. NON-CPI: N2003-197120
DOC. NO. CPI: C2003-063947
TITLE: Specific nucleic acids or proteins as markers of **hepatocellular carcinoma**, useful for **diagnosis**, treatment and drug screening.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): DEBUSCHEWITZ, S; JOBST, J; KAISER, S
PATENT ASSIGNEE(S): (DEBU-I) DEBUSCHEWITZ S; (JOBS-I) JOBST J; (KAIS-I) KAISER S
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003010336	A2	20030206	(200324)*	GE	98

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

DE 10136273 A1 20030213 (200324)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003010336	A2	WO 2002-EP8305	20020725
DE 10136273	A1	DE 2001-10136273	20010725

PRIORITY APPLN. INFO: DE 2001-10136273 20010725
AB WO2003010336 A UPAB: 20040226
NOVELTY - Use of specific nucleic acids (I), or polypeptides (II) encoded by them, as markers for hepatocellular **carcinoma** (HCC), is new.
DETAILED DESCRIPTION - Use of specific nucleic acids (I), or polypeptides (II) encoded by them, as markers for hepatocellular **carcinoma** (HCC). (I) is:
(i) any of about 1100 genes (tabulated);
(ii) an equivalent of (i) within the degeneracy of the genetic code;
(iii) a fragment of (i) or (ii) containing at least 20, best 100, nucleotides;
(iv) a sequence that hybridizes to (i)-(iii) under stringent conditions; or
(v) the complement of (i)-(iv).
INDEPENDENT CLAIMS are also included for the following:
(1) **diagnosis** of HCC using at least one (I) as probe;
(2) treatment of HCC by modulating the amount of at least one (I);

(3) HCC-specific cluster containing at least 60 (I); and
(4) expression profile associated with HCC containing at least 60 (I).

ACTIVITY - Cytostatic; Hepatotropic; Virucide; Antiinflammatory. No biological data is given.

MECHANISM OF ACTION - Modulation of gene expression/protein activity.

USE - (I) and (II) are useful for **diagnosis** and treatment of HCC, also for identifying new agents for treatment. They can also be used for differential **diagnosis** between HCC caused by hepatitis B or hepatitis C viruses, and HCC and cholangiocellular **carcinoma** (claimed), or, not claimed, between benign and malignant liver **tumors** (adenoma/**carcinoma**); between metastases to liver of bowel **cancer** and HCC; and between alcohol-associated and other forms of HCC. They may also be used to stage **cancers**.

Dwg.0/7

ED 20030410

L87 ANSWER 36 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-620030 [59] WPIDS
DOC. NO. CPI: C2003-169196
TITLE: Calculating the risk of developing **cancer** e.g. **colorectal cancer**, comprises obtaining a sample derived from an individual, analyzing polymorphisms of the **Midkine** gene and calculating the risk of developing **cancer** based on the polymorphisms.
DERWENT CLASS: B04 D16
INVENTOR(S): AHMED, K M; KUWANO, H; SHINOZAWA, T; SHITARA, Y; TAKENOSHITA, S
PATENT ASSIGNEE(S): (KUDO-I) KUDOH N; (KUDO-I) KUDO T; (AHME-I) AHMED K M; (KUWA-I) KUWANO H; (SHIN-I) SHINOZAWA T; (SHIT-I) SHITARA Y; (TAKE-I) TAKENOSHITA S
COUNTRY COUNT: 35
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1314787	A2	20030528	(200359)*	EN	19
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
CA 2408471	A1	20030526	(200359)	EN	
CN 1421532	A	20030604	(200359)		
JP 2003159074	A	20030603	(200359)		13
US 2003149534	A1	20030807	(200359)		
KR 2003043721	A	20030602	(200366)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1314787	A2	EP 2002-26076	20021122
CA 2408471	A1	CA 2002-2408471	20021121
CN 1421532	A	CN 2002-152872	20021126
JP 2003159074	A	JP 2001-359503	20011126
US 2003149534	A1	US 2002-301840	20021122
KR 2003043721	A	KR 2002-73765	20021126

PRIORITY APPLN. INFO: JP 2001-359503 20011126
AB EP 1314787 A UPAB: 20030915

NOVELTY - Calculating the risk of onset of **cancer** in an individual, comprising:

(a) obtaining a sample derived from the individual;

(b) analyzing polymorphisms of the **Midkine** gene; and

(c) calculating the risk of onset of **cancer** based on the polymorphisms, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a program for calculating the risk of onset of **cancer** in an individual;

(2) a calculating device, comprising:

(a) a storage unit for storing a table corresponding to a genotype with the risk of the onset of **cancer**;

(b) an inputting unit for inputting information of the genotype of MK808;

(c) a calculation unit for calculating the risk of onset of **cancer**, based on the genotype inputted through the inputting unit and the table stored by the storage unit; and

(d) a display unit for displaying the result of the calculation unit; and

(3) a DNA micro array, which contains at least one polynucleotide, as a nucleic acid probe to determine the genotype of MK808.

USE - The method, program, calculating device and DNA micro array are useful for calculating the risk of colorectal **cancer** in an individual (claimed).

ADVANTAGE - The method is simple and effective in anticipating the risk of **cancer**.

Dwg.0/7

ED 20030915

L87 ANSWER 37 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 1999-479186 [40] WPIDS

DOC. NO. CPI: C1999-141049

TITLE: **Midkine-binding** protein, useful for screening drug candidates for treatment of **cancers**, **cancer** metastasis, inflammation and Alzheimer's disease.

DERWENT CLASS: B04 D16

INVENTOR(S): IKEMATSU, S; KADOMATSU, K; MURAMATSU, T; SAKUMA, S

PATENT ASSIGNEE(S): (MEIP) MEIJI MILK PROD CO LTD; (MURA-I) MURAMATSU T

COUNTRY COUNT: 24

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9938971	A1	19990805	(199940)*	JA	36
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA CN JP KR US					
AU 9920765	A	19990816	(200002)		
JP 2000529431	X	20021002	(200270)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9938971	A1	WO 1999-JP423	19990202
AU 9920765	A	AU 1999-20765	19990202
JP 2000529431	X	WO 1999-JP423	19990202
		JP 2000-529431	19990202

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9920765	A	Based on	WO 9938971
JP 2000529431	X	Based on	WO 9938971

PRIORITY APPLN. INFO: JP 1998-35518 19980202

AB WO 9938971 A UPAB: 19991004

NOVELTY - A **midkine**-binding protein isolated from brain cell extract by immunoprecipitation with anti-**midkine** antibody is new.

DETAILED DESCRIPTION - DETAILED DESCIPTION - The novel protein is characterized by the following;

(a) being able to bind with **midkine** or heparin-binding **midkine**;

(b) not being able to bind with an antagonistic phosphotyrosine phosphatase zeta polyclonal antibody;

(c) being a membrane protein on cell surface; and

(d) without sensitivity towards heparitinase I, heparitinase II, heparitinase III, ketanase and condroitinase.

INDEPENDENT CLAIMS are also included for the following;

(i) the preparation of a **midkine**-binding protein by the following steps, (a)-(e):

(a) incubating a **midkine** binding protein-expressing animal cell with **midkine**;

(b) dissolving the cell in its solvent;

(c) adding anti-**midkine** polyclonal antibody and a support adsorbed with a protein that has affinity towards the antibody;

(d) formation of an immunocomplex containing anti-**midkine** polyclonal antibody, **midkine**, **midkine**-binding protein and the support; and

(e) isolation of the **midkine**-binding protein from the immunocomplex;

(ii) a DNA encoding the protein;

(iii) a vector containing the DNA;

(iv) a transformant that can maintain the vector;

(v) a method for producing the protein by culturing the transformant;

(vi) an antibody that can bind with the protein;

(vii) a screening method for selection of compound with inhibitory activity against the binding of the protein with **midkine** by;

(a) contacting the above protein or its part peptide and **midkine** to detect binding activity of the protein or its peptide; and

(b) comparing the binding activity with or without the test compound(s), with selection of compound(s) that can lower the binding activity;

(viii) a screening method for selecting agonists of the protein binding by;

(a) contacting the above protein or its part peptide with an expressing cell and the test compound(s) to detect the compound(s) with cell stimulation activity; and

(b) selecting compound(s) with practically identical cell stimulation activity as **midkine**;

(ix) a screening method for antagonists of the protein binding by

(a) contacting the above protein or its part peptide with an expressing cell in the presence of the test compound(s) and **midkine**, with detection of cell stimulation activity; and

(b) selecting compound(s) that can lower the cell stimulation activity; and

(x) a method for screening agonists or antagonists that have

midkine-induced cell stimulation activity which can be achieved by potentiating the phosphorylation of serine residue in the above protein or its part peptide.

ACTIVITY - Binding specifically to **midkine**.

MECHANISM OF ACTION - Midkine binder.

USE - The novel protein can bind with a midkine or heparin-binding growth factor midkine, which is useful in screening candidate compounds for drugs including cancer-therapeutic agents, preventives for cancer metastasis, anti-inflammatory agents and drugs for Alzheimer's disease.

Dwg.0/8

ED 19991004

L87 ANSWER 38 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1999-312872 [26] WPIDS
DOC. NO. CPI: C1999-092336
TITLE: Bioactive materials for modulating heparin-**binding** growth factor activity and targeted drug delivery.
DERWENT CLASS: B04 B07
INVENTOR(S): GALLAGHER, J T; PYE, D A
PATENT ASSIGNEE(S): (CANC-N) CANCER RES CAMPAIGN TECHNOLOGY
COUNTRY COUNT: 82
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9921588	A1	19990506	(199926)*	EN	96

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9910391 A 19990517 (199939)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9921588	A1	WO 1998-GB3201	19981028
AU 9910391	A	AU 1999-10391	19981028

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9910391	A	Based on	WO 9921588

PRIORITY APPLN. INFO: GB 1997-22604 19971028

AB WO 9921588 A UPAB: 19990707

NOVELTY - Bioactive materials comprise conjugate of (a) heparin-binding protein or polypeptide growth factor and (b) heparin or heparan sulfate (HS) of oligosaccharide coupled together through covalent bonds.

DETAILED DESCRIPTION - INDEPENDENT CLAIM are also included for

(1) A one-step preparation of bioactive material by treating HS oligosaccharide preparation with crosslinking reagents to form succinimide ester derivative in presence of growth factor and purifying;

(2) A pharmaceutical formulation comprising the above bioactive material; and

(3) A method for manufacturing a medical preparation comprising the

above bioactive material;

ACTIVITY - Healing promotion; tissue repair promotion; cell growth control; cell proliferation control.

MECHANISM OF ACTION - HB-EGF modulation; FGF inhibitor; FGF stimulator. Binding affinity of bFGF-oligosaccharide conjugates was checked by filter-binding assay. Native growth factor or growth factor/HS oligosaccharide conjugate material (4 mu g) was applied to nitrocellulose membrane filters in binding buffer (10 mM Tris-HCl; pH 7.3). The filters were washed with 2M sodium chloride (NaCl; 10 ml) in binding buffer to remove any non-crosslinked oligosaccharide present and were then equilibrated by washing with binding buffer. Radio-labeled 3H-HS was then applied in binding buffer (5 ml) and cycled through the filter three times. The filters were then washed with binding buffer (120 ml) to remove unbound material and bound HS was released by sequential washing first with three 5-ml aliquots of 0.3M NaCl followed by three 5-ml aliquots of 2M NaCl in binding buffer. Fractions (5 ml) were collected and radio-labeled eluted material quantified by scintillation counting. The results showed the complex to have no high or low affinity binding capacity for HS indicating that the oligosaccharide conjugate is covalently linked into the growth factor's HS binding site, resulting in the site being completely obscured from further HS interactions.

USE - Used in therapeutic pharmaceutical formulations to modulate heparin-binding growth factor activity in mammals and deliver drug or other therapeutic agent to mammals (claimed). Used to modulate growth factor activity and for targeted drug delivery in course of therapeutic treatment (claimed). Used to modify drugs or prodrugs to facilitate administration to mammals and targeted delivery to cells with specific growth factor receptors (claimed). Used as active FGF-activity stimulating agent to promote healing or tissue repair in mammals in connection with wound healing, bone healing, nerve regeneration, duodenal or venous ulcers, ocular and retinal disorders, atherosclerosis, ischemia or other conditions requiring tissue repair or to protect tissues against serious damaged during radiation treatment. Used as active FGF-activity inhibitor to control or reduce cell growth or proliferation in mammals in connection with diabetic retinopathy, capsular opacification, proliferative vitreoretinopathy, **tumor** angiogenesis, **cancer**-cell growth and metastasis, rheumatoid arthritis, degenerative muscular disorders (mild muscular dystrophy), Alzheimer's disease, viral infections (Herpes Simplex type 1), restenosis following angioplasty other conditions in which FGF activity inhibition is required.

ADVANTAGE - Covalent bonding between growth factor and oligosaccharide still allows growth factor to bind to its cell surface signal-transducing receptors on target cells and even when diminished, still mimics, to some extent, that of unbound or native growth factor. More resistant to proteolytic degradation and thermal inactivation. Oligosaccharide is varied to produce effects of stimulation/enhancement or inhibition of the growth factor's normal activity. The direct covalent linking of the growth factor to the oligosaccharide provides better bioavailability and enhanced targeting.

dp12/basic FGF (bFGF) crosslinked monomer conjugates and native bFGF (0.5 mu g) were mixed in phosphate-buffered saline (50 mu l) containing, as detergent, 3-((cholamidopropyl)-dimethylammonio)-1-propane-sulfonate (CHAPS; 1%) before addition of trypsin (4 mu l; 2 mg/ml). The reaction mixtures were incubated for 24 hours at 37 deg. C, aliquots were removed and analyzed by 12% SDS polyacrylamide electrophoresis (PAGE) and immunodetection. Results showed that dp12/bFGF crosslinked monomer conjugates were significantly more resistant to proteolytic degradation compared to the native bFGF, which was extensively degraded.

ED 19990707

```
=> file home
FILE 'HOME' ENTERED AT 17:59:46 ON 02 MAR 2004

=>
```